# A Computer Program for the Multivariate and Graphical Monitoring of Acid-Base Data in an Intensive Care Unit

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*Monitoring the arterial acid-base status of ICU patients is done by measuring and calculating the acid-base variables pH, the partial pressure of carbon-dioxide ($P_{CO_2}$) and the bicarbonate-ion concentration ($[HCO_3^-]$). Univariate normal reference ranges exist for these values. However, it is well known that an exact linear relationship exists between pH, the logarithm of $P_{CO_2}$ and the logarithm of $[HCO_3^-]$ values. We developed a computer program for the multivariate evaluation and graphical monitoring of these values in an intensive care setting that takes this intrinsic two-dimensionality into account. A composite index is introduced for the monitoring of all three laboratory values. Moreover, using this index, a multivariate statistical reference region based on an unselected population of ICU patients was derived.*

## INTRODUCTION

Intensive care medicine of today is characterized by a voluminous production of measured and calculated parameters. Continuous monitoring of vital signs, laboratory values, ventilator settings, etc., generates a vast and never ending stream of data to be evaluated and interpreted by ICU personnel. The main role of computers in the ICU is to support clinicians and nurses in their evaluation and interpretation process by managing, manipulating and displaying data. Integrated database management systems for the ICU are being built and evaluated [1,2]. Expert systems exist for several domains in intensive care medicine [3,4]. Signal processing algorithms are developed, tested and applied for several monitoring systems.

Especially in the ICU there is a great focus on how information should be presented to clinicians and nurses. It has been shown that a clear graphical representation of data is superior to tabular, non-graphical ways of representation [5,6]. Methods and approaches for the graphical display of numerical data are being designed and tested [7,8,9]. Because it is difficult for the clinician to memorize all the data, especially the display of previous data together with the current is very useful in an intensive care setting [2].

We developed and implemented a model that supports the interpretation of acid-base data in an intensive care unit that addresses some of the points discussed above. Typically three laboratory values are used to diagnose an ICU patient's arterial acid-base status; the arterial pH, the partial pressure of arterial carbon dioxide ($P_{CO_2}$) and the arterial bicarbonate-ion concentration ($[HCO_3^-]$). A linear relationship exists between pH, log $P_{CO_2}$ and log $[HCO_3^-]$ as described by the Henderson-Hasselbalch equation [10]:

$$pH = pK' + \log([HCO_3^-] / \alpha P_{CO_2}) \qquad [1]$$

with $pK' = 6.10$ and $\alpha = 0.225$ mmol/l/kPa (or 0.03 mmol/l/mmHg).

Geometrically this means that triplets of measured pH, the logarithm of measured $P_{CO_2}$ and the logarithm of calculated $[HCO_3^-]$ will be restricted to a plane in measurement space. Hence, only two of the three acid-base variables suffice to describe the acid-base status [11]. We applied a multivariate statistical technique called Principal Component Analysis (PCA) to derive reference values and to generate a chart for display of pH, $P_{CO_2}$ and $[HCO_3^-]$ values that is consistent with the linear relationship between these acid-base variables. This paper will discuss the model and the development of a prototype acid-base monitoring system that is based on this model.

## THE MODEL

### Principal Component Analysis

PCA is a multivariate statistical technique that can be used to reduce the dimensionality of a multivariate distribution. We performed a PCA on 1500 standardized triplets of pH, log $P_{CO_2}$ and log $[HCO_3^-]$ values from patients in a respiratory ICU of the university Hospital Dijkzigt, Rotterdam. No specific inclusion or exclusion criteria were used. In linear algebraic terms, PCA finds a matrix of transformation $U$, which transforms the 1500 original vectors **x** (consisting of pH, log $P_{CO_2}$ and log $[HCO_3^-]$) into vectors **y** in such a way that the variance-covariance matrix $W = UVU^t$ of the transformed vectors **y** is diagonal ($V$ is the variance-covariance matrix as determined on the original distribution of 1500 pH, log $P\mathrm{CO}_2$ and log $[HCO_3^-]$ triplets and the superscript $t$ stands for the transposition of a matrix) [12,13]. The total variance in the transformed distribution is equal to the variance in the original distribution. If $U$ is constrained to be a unitary matrix, the axes of the coordinate system of the transformed distribution ($PC_1$, $PC_2$ and $PC_3$) have two important characteristics; 1. they are uncorrelated and 2. they are ordered by their variances.

Based on this definition of PCA, since pH, log $P\mathrm{CO}_2$ and log $[HCO_3^-]$ are linearly related, it is obvious that the first two principal component axes ($PC_1$ and $PC_2$ ) explain the major part of the variance in the original distribution of 1500 triplets. We found that 99.9 % of the total variance in the original distribution could be explained by the coordinate axes $PC_1$ and $PC_2$ after PCA. The remaining 0.1 % variation along the $PC_3$ axis can be attributed to round-off and measurement errors [13].

The described PCA transformation forms the basis of the proposed acid-base chart. Transforming pH, log $P\mathrm{CO}_2$ and log $[HCO_3^-]$ of a new observation with the transformation matrix $U$ and plotting the resultant $PC_1$ and $PC_2$ values, enables the representation of this observation onto a two-dimensional plane without loss of information. To have a standard appearance of the chart an extra rotation was added to the transformation matrix $U$ in order to display the original pH-axis always in the horizontal direction. The values of an observation projected on the rotated $PC_1$ and $PC_2$ axes will be further denoted as $pc_1$ and $pc_2$.

**Bivariate Reference Region**

Using three separate univariate reference ranges for pH, $P\mathrm{CO}_2$ and $[HCO_3^-]$ while only two of these variables are free to change independently is illogical [11]. Moreover, from a fundamental statistical point of view the use of multiple univariate reference ranges is erroneous because it ignores possible correlations between the variables used [14]. We therefore derived a bivariate reference region for pH, $P\mathrm{CO}_2$ and $[HCO_3^-]$ that is based on the distribution of $pc_1$ and $pc_2$ after the principal component transformation as decribed in the preceding section.

For each of the 1500 $pc_1$ and $pc_2$ values after the transformation, the squared Mahalanobis-distance ($D_m^2$) was calculated [14];

$$D_m^2 = (\mathbf{y}-\mathbf{m})^t S^{-1} (\mathbf{y}-\mathbf{m}) \qquad [2]$$

where **m** is the estimated mean vector (consisting of the means of $pc_1$ and $pc_2$), $S$ is the estimated variance-covariance matrix (consisting of the variances and covariances of $pc_1$ and $pc_2$) and **y** is an observation vector (consisting of $pc_1$ and $pc_2$ of an observation). **m** and $S$ are called the modelparameters. The superscript $t$ stands for the transposition of a column-vector to a row-vector.

The squared Mahalanobis-distance is the multivariate analog of the univariate standard deviation score. If a bivariate distribution is bivariately normal (or Gaussian), the calculated $D_m^2$'s will follow a chi-square ($\chi^2$) distribution with two degrees of freedom. The 95 % cut-off value of such a chi-square distribution corresponds with a chi-square value of 5.99. Thus, a calculated $D_m^2$ for a single observation larger than 5.99 implies that the observation is located outside the 95 % bivarate reference region.

For the squared Mahalanobis-distance to be valid as a multivariate index of abnormality, the distribution must be bivariately normal. With a double iterative method described by Gelsema et al. we established a bivariately normal distribution from the original distribution of 1500 $pc_1$ and $pc_2$ values [15].

Since it measures the (weighted) distance from the population mean to an observation, the Mahalanobis-distance ($D_m$) is also a potential parameter for monitoring the severity of an acid-base status.

## THE COMPUTER PROGRAM

A stand-alone prototype acid-base monitoring system has been developed that is based on the described model. The prototype has been written in Visual Basic for the Microsoft Windows environment. The program offers user-friendly entry of patient- and acid-base data. From a special initialization file the program reads the necessary transformation matrix that has been defined on the patient data set as described in the section *Principal Component Analysis* and the modelparameters $S$ and **m** that have been defined on the same patient data set as described in the section *Bivariate Reference Region.* For each blood gas entry, it calculates $pc_1$ and $pc_2$ and plots these values in the two dimensional acid-base map. Values of the original acid-base variables may also be read off the chart. Furthermore, it calculates and displays the Mahalanobis-distance ($D_m$.) in a trend-plot.

In figure 1 the main screen of the program is shown with data of a patient at the respiratory ICU of the university Hospital Dijkzigt, Rotterdam. AB stands for 'Actual Bicarbonate' ( = $[HCO_3^-]$).

The first bloodgas analysis shows a severe, compensated metabolic acidosis. The acid-base path shows that this patient has been brought back to more acceptable values within a five day period.

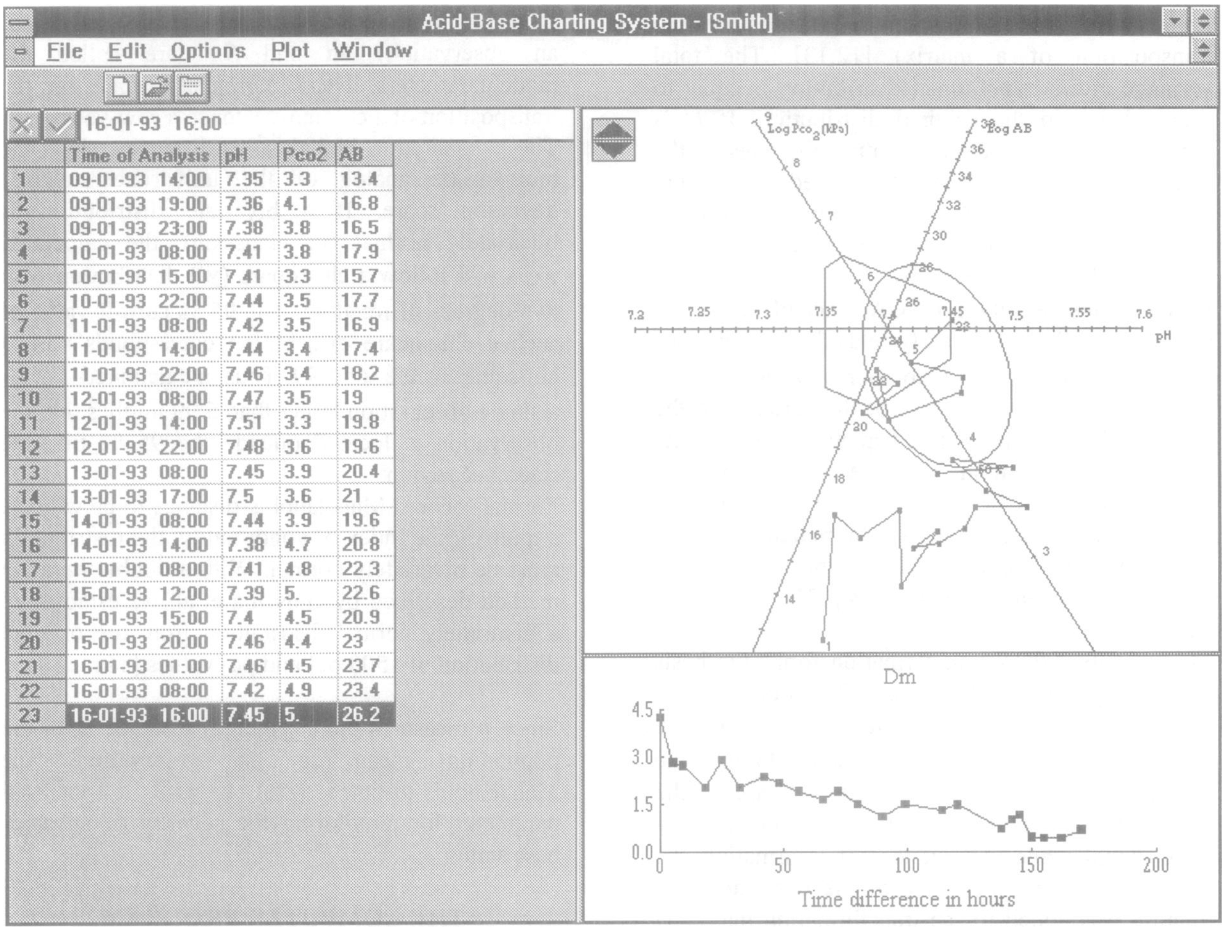


Figure 1. Main screen of the prototype acid-base monitoring system. At the left side the data grid is shown where the acid-base data of a patient can be filled in. In the upper right corner the new chart can be seen with the acid-base path of a patient. The hexagon shaped figure in the middle of the chart is the reference region when univariate ranges of mean plus and minus 2 standard deviations are applied. The ellipse represents the 50% equal density ellipse. In the lower right corner the trend chart of the Mahalanobis distance is drawn. On the y-axis the actual Mahalanobis distance and on the abscissa the difference in hours between the specific analysis at hand and the first analysis.

The first analysis and last analysis are numbered 1 and 23, respectively in the chart. This gradual trend toward more acceptable levels can also be appreciated from the trend-plot of $D_m$ at the bottom of the screen.

The hexagon-shaped figure at the center of the chart represents the standard multiple univariate reference region from literature. The ellipse represents the bivariate reference region that is based on the used patient data set. This ellipse encloses the 50 % bivariate confidence region, meaning that 50 % of the bivariate patient distribution is located within this ellipse. Notice that this ellipse is quite shifted from the standard multiple univariate reference region towards more alkaline values. Also note that for each plotted point, the original laboratory values can be found when the observation is projected perpendicular to the respective original axes.

## DISCUSSION

A paradox exists for the interpretation of acid-base data. Traditionally, the three laboratory values pH, $P_{CO_2}$ and $[HCO_3^-]$ are used for the diagnosis of an acid-base status although the system is intrinsically two-dimensional. We applied PCA on a ICU patient distribution of pH, $P_{CO_2}$ and $[HCO_3^-]$ values for the derivation of a bivariate reference region for this patient population. A major advantage of this model for the establishment of multivariate reference regions is that all three acid-base variables are included in the analysis and are represented in the triaxial chart but the statistical treatment of the data is in concordance with the linear relationship between the three acid-base variables. Moreover, no prior knowledge is needed about the formula with which the $[HCO_3^-]$ values are calculated from measured pH and $P_{CO_2}$ values.

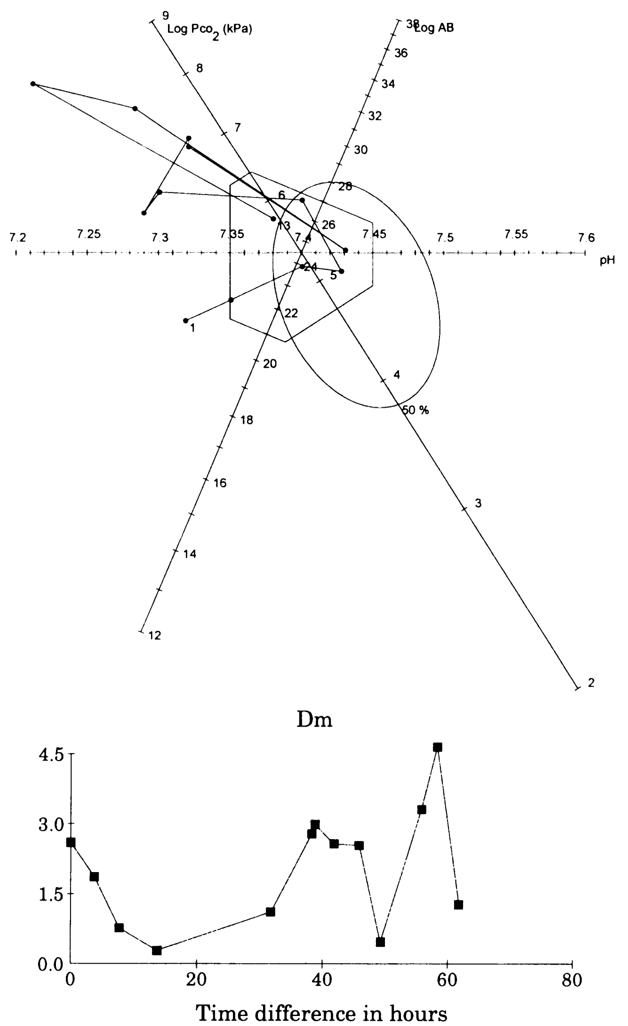


Figure 2. Acid-base chart and trend plot of Mahalanobis distance (Dm) of a patient of the respiratory ICU of the Academic Hospital Dijkzigt, Rotterdam. Log $P_{CO_2}$ and Log AB stand for the logarithm of $P_{CO_2}$ in kPa and the logarithm of [$HCO_3^-$], respectively.

A 72 year old male patient with COPD (chronic obstructive pulmonary disease) was admitted to the respiratory ICU with a respiratory insufficiency. He was immediately intubated and mechanical ventilation was started. A first attempt to "wean" the patient from the ventilator between t = 32 hours and t = 38 hours resulted in a sudden increase in Mahalanobis distance Dm. Dm remained high until weaning was stopped between t = 45 hours and t = 49 hours. Just before t = 55 hours, weaning was restarted, resulting again in a high Dm. Although it was clear that the patient was not able to regulate his acid-base status breathing spontaneously, an extubation was tried which immediately resulted in a severe respiratory acidosis. The patient was re-intubated and the arterial blood gas values normalized with the aid of the ventilator. Further attempts to wean the patient from the ventilator were eventually successful (not shown).

In order to answer the question whether this patient-based bivariate reference region could be useful in an intensive care setting, one should first consider the mechanisms that shape a reference population. One of those mechanisms is the nature of the ICU from which the reference population is taken. Arterial acid-base data from a neonatal ICU will be quite different from acid-base data coming from a respiratory ICU for adults. Another mechanism that may be at play in shaping a reference population is the fact that clinicians from different ICU's may use different targets for arterial blood gas values. Therefore, a multivariate reference region based on an ICU population is not only patient-based but also clinic-dependent. It gives an indication which of the patients in one particular ICU are most in need of care.

We also introduced a new parameter for monitoring the severity of acid-base states. The Mahalanobis-distance enables the monitoring of the original three laboratory values with only a single parameter. Monitoring the acid-base status with this single multivariate index may well be advantageous for ICU personnel because of its simplicity. In a future acid-base monitoring system only a single threshold needs to be set instead of three separate thresholds for all laboratory acid-base variables. Also, using the Mahalanobis-distance as the monitoring parameter could substantially reduce the number of false-positive alarms. It should be noted here that the proposed composite index does not add new concepts to the problem of interpreting acid-base data. We merely present another statistical tool for the analysis of acid-base data that deals with the fundamental problems that are associated with the simultaneous analysis of more that one variable. The proposed technique has no impact on the way a clinician interprets the acid-base data of a patient but patient outcome could be indirectly influenced because of the possible reduction in false positive alarms and the simplicity of analyzing a single parameter, giving the clinician more time for other aspects of patient care.

Another important result of the applied PCA is the ability to generate a display of acid-base data that is consistent with the linear relationship between the data. It should be mentioned that as early as in 1935 Shock and Hasting proposed a similar placement of original axes to study the displacement of acid-base states in various conditions [16]. Even in 1974 this elegant way of representing acid-base data was favoured by Rispens, Zijlstra and van Kampen [17]. Both authors also state that this way of representing acid-base data never found its way to regular use. The reason for this is probably not located in the nature of the chart itself. The interpretation of acid-base data has been the subject of numerous acid-

base charts to facilitate the interpretation and evaluation of acid-base data. Until today none of these acid-base charts are used in the intensive care unit on a regular basis.
At the present moment the graphical display of acid-base data may not be essential but in the near future this could indeed become a crucial item. New techniques for real-time intra-arterial monitoring of acid-base data are now being developed and clinically tested [18,19]. At first these techniques shall only be used in critically ill patients but in time these real-time bloodgas analyzers could become standard equipment on an ICU. Real-time measuring of the acid-base variables produces an enormous amount of data that must be interpreted by the ICU personnel. Graphical monitoring devices for acid-base data will therefore become indispensable in the intensive care setting of tomorrow.

At this moment a clinical trial is being prepared to evaluate the usefulness of patient-based bivariate reference regions and the acid-base chart in a clinical setting. With an intervention study we will investigate the impact of introducing the developed computer program on an ICU.

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